ORIGINAL ARTICLE

Admission hyperglycemia in acute myocardial infarction is associated with an increased risk of arrhythmias: A systematic review and meta-analysis

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Abstract

Background: Admission hyperglycemia (AH) has shown to be associated with higher mortality rates in acute myocardial infarction (AMI). Malignant arrhythmia is one of the causes of death in AMI; however, it is unclear whether AH is associated with an increased arrhythmia risk. We conducted this systematic review and meta-analysis to assess the association between AH and arrhythmias in AMI.

Methods: We searched MEDLINE, and Embase databases from inception to September 2021 to identify studies that compared arrhythmia rates between AMI patients with AH and those without. Arrhythmias of interest included ventricular tachyarrhythmias (VA), atrial fibrillation (AF), and atrioventricular block.

Results: Thirteen cohort studies with a total of 12,898 patients were included. AH was associated with a higher risk of overall arrhythmias (18% vs 10.3%, pooled odds ratio [OR] = 1.89, 95% confidence interval [CI]: 1.39–2.56, $P < .001$), VA (16.4% vs 11.1%, pooled OR = 1.56, 95% CI: 1.11–2.18, $P = .01$), and new onset AF (17.8% vs 6.4%, pooled OR = 2.13, 95% CI: 1.4–3.25, $P < .0010$. Subgroup analysis of diabetes status regarding overall arrhythmias showed that the increased risk of arrhythmias in the AH group was consistent in both patients with a history of diabetes (18% vs 12.5%, pooled OR = 2.33, 95%CI: 1.2–4.52, $P = .004$) and without (15.7%. vs 9% pooled OR = 1.35, 95% CI: 1.1–1.66, $P = .013$).

Conclusion: Admission hyperglycemia in AMI was associated with the increased risk of arrhythmias, regardless of history of diabetes mellitus.

KEYWORDS

acute myocardial infarction, arrhythmia, hyperglycemia

1 | INTRODUCTION

Admission hyperglycemia (AH) is common in patients with critical illness including acute myocardial infarction (AMI).[1,2] Prior studies reported that the prevalence of AH ranged from 25% to more than 50% in patients with acute coronary syndrome (ACS).[2–4] Mechanisms of stress-induced hyperglycemia are complex. The human body physiologically responds to stress by increasing the release of stress hormones including glucagon, cortisol, catecholamine, and proinflammatory cytokines through stimulating the sympathoadrenal system, resulting in hyperglycemia.[5]

Hyperglycemia creates oxidative stress, promotes further coagulation, and induces apoptosis leading to increased tissue damage.[6,7] This could explain why hyperglycemia is associated with worse outcomes in patients with acute illness including AMI.[8] The previous meta-analysis showed that AH was a strong predictor of worse short- and long-term outcomes in AMI patients who underwent primary percutaneous coronary intervention (pPCI).[9–11] However, it's unclear whether AH is associated with higher risks of arrhythmias in patients with AMI when compared to AMI patients with normoglycemia (NG). We conducted this meta-analysis and systematic review to determine whether AH in patients admitted for AMI is associated with an increased risk of arrhythmias.

2 | METHODS

2.1 | Search strategy

Two investigators (AT and MB) independently performed a systematic search of the MEDLINE, and Embase databases from inception to September 2021 using a search strategy including the terms "hyperglycemia," "acute myocardial infarction," "arrhythmia," "acute ventricular tachycardia/fibrillation," "atrial fibrillation," and "atrioventricular block" as described in Table S1. We hand-searched the bibliographies of selected studies and meta-analyses to identify further eligible studies. Only full articles in English were included.

2.2 | Inclusion criteria

The eligible criteria included the following:

1. Cohort studies (prospective or retrospective), case–control studies, experimental studies, or randomized controlled trials (RCTs) that reported and compared the incidence of arrhythmias including ventricular tachycardia (VT), ventricular fibrillation (VF), atrial fibrillation (AF), and atrioventricular block (AV block) between the AH group and the NG group in patients with AMI (ST-segment elevation myocardial infarction [STEMI] and non-ST-segment elevation myocardial infarction [NSTEMI]). Studies that included patients with unstable angina and supraventricular tachycardia including atrial tachycardia, atrioventricular nodal

reentry tachycardia, and atrioventricular reentrant tachycardia were excluded from this meta-analysis.
2. Relative risk, odds ratio (OR), hazard ratio, incidence ratio with 95% confidence intervals (CI), or sufficient raw data to calculate effect size must be provided.

2.3 | Data extraction and quality assessment tool

Two authors (AT and ST) independently extracted the data from included studies, with disputes resolved by consensus following discussion with a third author (JK). Included observational studies were assessed using the Newcastle-Ottawa Scale (NOS) for quality assessment.[12] The Cochrane Collaboration tool for assessing the risk of bias was used to evaluate the quality of each randomized controlled trial by assessing as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other).[13]

2.4 | Outcomes

1. Primary outcomes: rates of overall arrhythmias of interest.
2. Secondary outcomes: rates of new-onset AF and ventricular tachyarrhythmias (VT/VF).

2.5 | Definitions

AMI was defined as the detection of a rise and/or fall cardiac troponin (cTn) value with at least 1 value above the 99th percentile and with at least one of the following: (1) AMI symptoms; (2) new ischemic pattern changes on electrocardiogram (ECG); (3) Development of pathological Q waves; (4) evidence of new loss of viable myocardium or new regional wall motion abnormality on imaging; (5) a coronary thrombus by angiography.[14] STEMI was defined by at least two contiguous leads with ST-segment elevation ≥2.5 mm in men <40 years, ≥2 mm in men ≥40 years, or ≥1.5 mm in women in leads V2–V3 and/or ≥1 mm in the other leads.[14] NSTEMI was defined as new ST-depression ≥0.5 mm in two contiguous leads and/or T inversion >1 mm in two contiguous leads with prominent R wave or R/S ratio >1.[14]

Admission hyperglycemia was defined as venous blood glucose or capillary blood glucose measured on admission greater than 140 mg/dL.[15] Each study defined AH differently as shown in Table 1.

Arrhythmias were defined as new-onset arrhythmias including VT, VF, AF, or AV block.

2.6 | Statistical analysis

This meta-analysis was performed using a random-effects model. The extracted studies were excluded from the analysis if they did

not justify an outcome in each cohort. OR was used to determine the difference in outcomes between the two groups. Q-statistic and I^2 statistic was used to assess evidence of heterogeneity.[16] The I^2 statistic ranges in value from 0 %to 100% ($I^2 < 25\%$, low heterogeneity; $I^2 = 25\%$–50%, moderate heterogeneity; and $I^2 \geq 50\%$, substantial heterogeneity).[17] Publication bias was assessed using a funnel plot, Begg's test, and Egger's test.[18,19] The $P < .05$ in publication bias tests was suggestive of publication bias. Sensitivity analysis was also performed to assess the influence of individual studies on overall meta-analysis, as described by Patsopoulos et al.[16,20] Sensitivity analysis and meta-regression analysis were performed. All analyses were conducted using Review Manager 5.1 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA software (version 14 STATA Corp, College Station, TX, USA).

3 | RESULTS

3.1 | Literature search

The initial literature search identified 1,130 studies from MEDLINE, and Embase databases. We excluded 296 studies because of duplication. Seven hundred eighty-seven studies were excluded as they were not cohort studies, case–control studies, experimental trials, RCTs, or did not study the population of interest. This left 47 studies for full-text review. Thirty-four studies were further excluded because of reasons given in the PRISMA flow diagram in Figure 1. Therefore, 13 studies were included in this meta-analysis.

3.2 | Description of included studies

A total of 13 studies from 2010 to July 2021 were included in this meta-analysis.[21–33] There were seven prospective cohort studies and six retrospective cohort studies. Seven studies were from Asia, five studies were from Europe, and one study was from the United States. The final analysis included a total of 12,898 patients (5151 in the AH group and 7775 in the NG group). Sixty-eight percent were male and 27% had a history of diabetes mellitus (DM). The baseline characteristics of the included studies are shown in Table 1.

3.3 | Quality assessment tool

The NOS of the included studies are described in Table S2.

3.4 | Meta-analysis results

3.4.1 | Overall arrhythmias

The primary outcome of overall arrhythmias was reported in 13 studies. Arrhythmias occurred 18% and 10.3% in the AH and the NG group, respectively. The AH group had significantly higher risks of overall arrhythmias (pooled OR = 1.89, 95%CI: 1.39–2.56, $P < .001$, $I^2 = 82\%$). As shown in Figure 2.

Secondary outcomes included VA and new-onset AF. VA was reported in eight studies and occurred 16.4% and 11.1% in the AH and the NG group, respectively. AH group had significantly higher risk of VA (pooled OR = 1.56, 95%CI: 1.11–2.18, $P = .01$, $I^2 = 70\%$). As shown in Figure 3. New-onset AF was reported in six studies. AF occurred 17.8% and 6.4% in AH and NG groups, respectively. The AH group was significantly associated with higher risks of new-onset AF (pooled OR = 2.13, 95%CI: 1.4–3.25, $P < .001$, $I^2 = 59\%$). As shown in Figure 4.

3.4.2 | Subgroup analysis

We performed a subgroup analysis of DM status which showed that patients in the AH group had higher rates of overall arrhythmias in both DM and non-DM groups. The overall arrhythmia rates in patients with DM were 18% and 12.5% in the AH and the NG group, respectively (pooled OR = 2.33, 95%CI: 1.2–4.52, $P = .004$, $I^2 = 67.1\%$). The overall arrhythmia rates in patients without DM were 15.7% and 9% in the AH and the NG group, respectively (pooled OR = 1.35, 95% CI: 1.1–1.66, $P = .013$, $I^2 = 0\%$). Subgroup analysis of definitions of AH found no association between different definitions of AH and the effect of AH on overall arrhythmias (Table S3).

3.4.3 | Sensitivity analysis

We conducted a sensitivity analysis for each outcome by excluding one study at a time to assess the stability of the results of the meta-analysis. For every outcome, none of the results were significantly altered, as the results were similar to that of the main meta-analysis, indicating that our results were robust.

3.4.4 | Publication bias

We investigated the effect of potential publication bias on overall arrhythmias by creating a funnel plot from included studies. The vertical axis of the funnel plot represents study size (standard error of log OR) while the horizontal axis represents effect size (log OR). The funnel plot showed symmetrical distribution which represented the absence of publication bias (Figure S1). We also performed Begg's and Egger's test to assess publication bias. There was no publication bias according to Begg's and Egger's tests (Begg's test, $P = .827$ and Egger's test; $P = .065$).

4 | DISCUSSION

This is the first systematic review and meta-analysis to date that assess the association between AH and risk of arrhythmias in patients

TABLE 1 Study characteristics

First author, year	Country	Study design	Total population/ male, n/%	Study population	Patients with known DM, %	AH cutoff, mg/dL (mmol/L)	Incidence of AH, n/%
Chen, 2014[21]	Taiwan	Retrospective cohort	959/82	Patients with STEMI undergoing PCI	31.9	140 (7.8)	542/56.5
Dziewierz, 2010[22]	Poland	Prospective cohort	607/58.5	Patients with AMI (STEMI and NSTEMI)	24.7	200 (11.1)	46/7.6
Ekmekci, 2014[23]	Turkey	Prospective cohort	503/87.9	Patients with STEMI after PCI	0	145 (8)	169/33.6
Huang, 2015[24]	China	Retrospective cohort	3359/74.3	Patiets with STEMI who received reperfusion therapy	27.2	190 (10.5)	820/24.4
Koracevic, 2008[25]	Serbia	Retrospective cohort	543/54.9	Patients with AMI (STEMI and NSTEMI)	25.8	145 (8)	200/36.8
Li, 2021[26]	China	Retrospective cohort	563/79.6	Patients with AMI (STEMI and NSTEMI)	12.6	126 (7)	250/44.4
Luo, 2014[27]	China	Retrospective cohort	253/0	Females with first STEMI or NSTEMI	34	200 (11.1)	84/33.5
Marenzi, 2010[28]	Italy	Prospective cohort	780/81.2	Patients with STEMI undergoing PCI	14	198 (11)	148/19
Nasution, 2020[29]	Indonesia	Cross-sectional followed by prospective cohort	110/80	Patients with AMI (STEMI and NSTEMI)	40	140 (7.8)	65/59
Sanjuan, 2011[30]	Spain	Prospective cohort	834/74	Patients with STEMI	33	140 (7.8)	455/54
Terlecki, 2013[31]	Poland	Prospective cohort	246/67.5	Patients with STEMI undergoing PCI	30.5	140 (7.8)	136/55.3
Tran, 2018[32]	United States	Retrospective cohort	4140/58	Patients with AMI (STEMI or NSTEMI)	36.1	140 (7.8)	2191/51.9
Yan, 2016[33]	China	Retrospective cohort	151/70.4	Patients with STEMI	38.3	145 (8)	45/20.1

Abbreviations: AF, atrial fibrillation; ACEI, angiotensin-converting enzyme inhibitors; AH, admission hyperglycemia; AMI, acute myocardial infarction; ASA, aspirin; AT, atrial tachycardia; AV, atrioventricular block; BB, beta-blocker; BBB, bundle branch block; DM, diabetes; EF, ejection fraction; HF, heart failure; N, number; N/A, not available; NG, normoglycemia; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, segment elevation myocardial infarction; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.

[a]Median.

with AMI, with or without a diagnosis of diabetes mellitus. We found that AH was associated with an increased risk of overall arrhythmias as described during the hospitalization after AMI, which was consistent regardless of diabetes status.

Previous literature showed a close link between DM and cardiovascular disease[34–36] and is well-known to be associated with lower survival rates in patients with AMI.[37] Recently, a few studies also reported the association between hyperglycemia in non-diabetes and worse outcomes. The meta-analysis by Singh et al. revealed that AH in patients with AMI admitted for primary angioplasty had higher mortality rates.[9] They also performed a subgroup analysis of non-diabetic patients, and the results were consistent with the main analysis. This meta-analysis aimed to focus on the effect of hyperglycemia and the risks of arrhythmias. Our meta-analysis found that hyperglycemia was associated with higher risks of overall arrhythmias in both patients with and without diabetes. However, further studies are warranted to support if arrhythmias are associated with a worse prognosis after AMI.

Arrhythmias of interest	PCI, %		HF, %		EF, %		ASA %		ACEI, %		BB, %		Statin, %	
	AH	NG	AH	NG	AH	NG	AH	NG	AH	NG	AH	NG	AH	NG
VF required defibrillation	100	100	3.3	2.4	53.7 ± 13.2	57.2 ± 11.9	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
VT, VF, AF, 2nd/3rd AV block	N/A	N/A	24.2	22.6	45[a]	49.2[a]	91	95	67	78	63	79	74	87
Severe VA	100	100	N/A	N/A	43.3 ± 9.8	46.6 ± 7.1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
High grade AV block (advanced 2nd AV block, 3rd AV block)	24.2	19.3	1.2	2.6	N/A	N/A	97	97	73	73	62	65	78	77
AF	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
AF	70	68	N/A	N/A	50 ± 10	52 ± 10	90	94	88	97	47	44	92	96
Malignant arrhythmias (VT, VF, 3rd AV block, AF)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
VF, AF	100	100	N/A	N/A	46[a]	51[a]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
VT, VF	N/A	N/A	N/A	N/A	46 ± 14.3	47 ± 13.1	N/A	N/A						
Malignant arrhythmias (VT, VF), paroxysmal, or persistent AF, complicated intraventricular conduction defects (Left or Right BBB), at least 2nd AV Block	15.5		N/A		51 ± 14		96		55		47		58	
2nd or 3rd AV block, AF, VF	100	100	N/A	N/A	47.5[a]	50[a]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
VT	42	51.6	28.1	17.1	N/A	N/A	92	94	73	68	91	92	N/A	N/A
VT, VF, AT, AF, Bradyarrhythmia (sinus bradycardia or AV block)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	32	

There are a few plausible mechanisms that may explain the association between hyperglycemia and arrhythmias. Hyperglycemia can cause impaired ventricular repolarization resulting in prolongation of QT interval, leading to ventricular arrhythmias.[2,38] The production of inflammatory cytokines in hyperglycemia via oxidative stress can also promote cardiac arrhythmias, such as AF.[39–42] Hyperglycemia is also associated with larger infarction sizes in different types of AMI, which is an acknowledged risk for VA and worse outcomes.[43,44] Autonomic dysfunction in hyperglycemia was found to be associated with new-onset AF.[45] The study by Agarwal and colleagues showed that low heart rate variability (HRV), which was a marker for cardiac autonomic dysfunction, was associated with higher risks of developing AF during the 20 years of follow-up.[46] Moreover, the hyperosmolar state in hyperglycemia can alter electrophysiological activity in myocytes, resulting in arrhythmias.[47]

We acknowledge a few limitations. First, this meta-analysis was mainly driven by observational studies which are subjected to bias. Second, each study used different definitions of AH. However, this
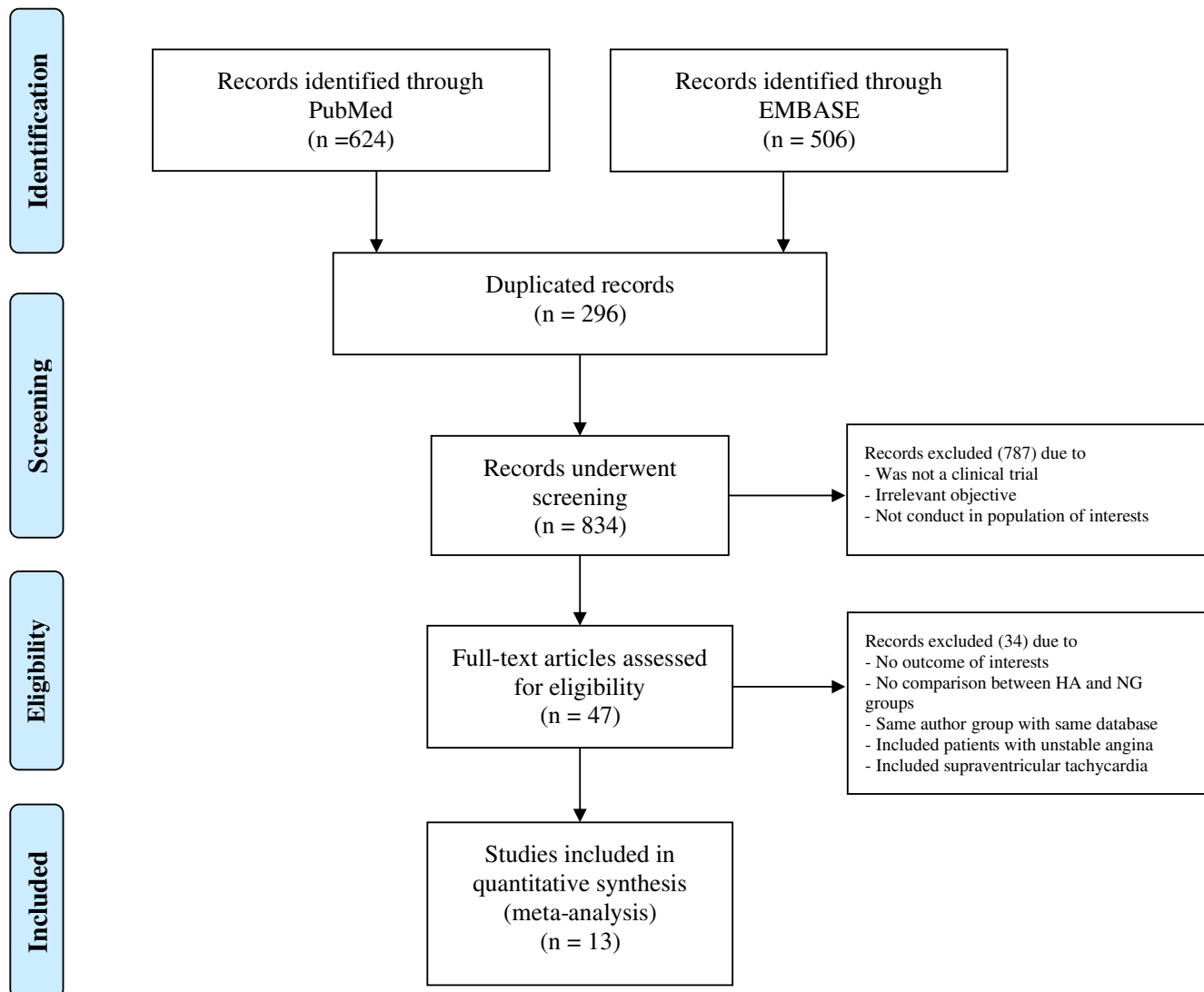
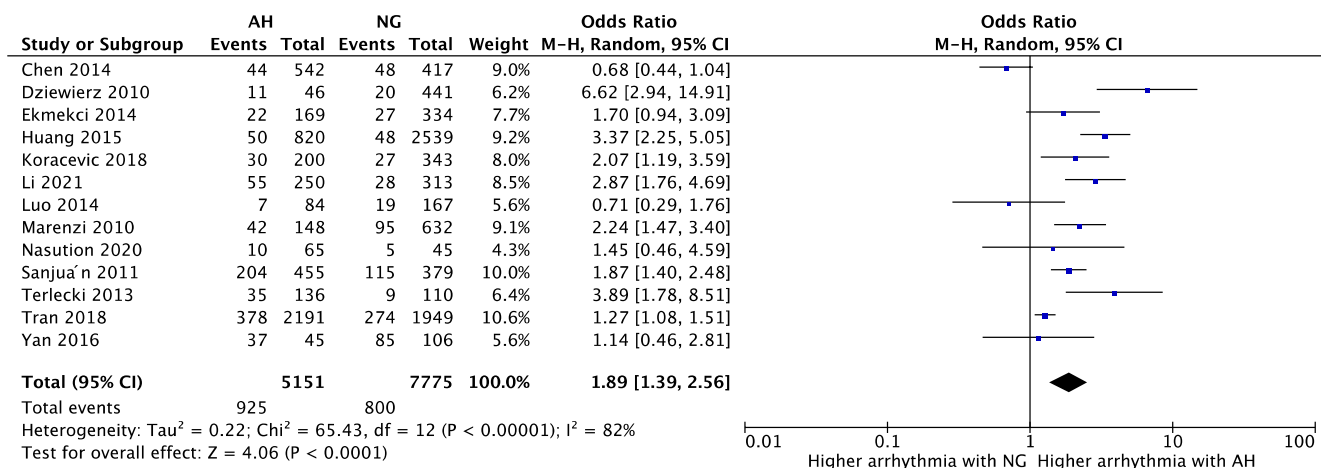**FIGURE 1** PRISMA flow diagram illustrating the study selection process

Study or Subgroup	AH Events	Total	NG Events	Total	Weight	Odds Ratio M–H, Random, 95% CI	Odds Ratio M–H, Random, 95% CI
Chen 2014	44	542	48	417	9.0%	0.68 [0.44, 1.04]	
Dziewierz 2010	11	46	20	441	6.2%	6.62 [2.94, 14.91]	
Ekmekci 2014	22	169	27	334	7.7%	1.70 [0.94, 3.09]	
Huang 2015	50	820	48	2539	9.2%	3.37 [2.25, 5.05]	
Koracevic 2018	30	200	27	343	8.0%	2.07 [1.19, 3.59]	
Li 2021	55	250	28	313	8.5%	2.87 [1.76, 4.69]	
Luo 2014	7	84	19	167	5.6%	0.71 [0.29, 1.76]	
Marenzi 2010	42	148	95	632	9.1%	2.24 [1.47, 3.40]	
Nasution 2020	10	65	5	45	4.3%	1.45 [0.46, 4.59]	
Sanjua´n 2011	204	455	115	379	10.0%	1.87 [1.40, 2.48]	
Terlecki 2013	35	136	9	110	6.4%	3.89 [1.78, 8.51]	
Tran 2018	378	2191	274	1949	10.6%	1.27 [1.08, 1.51]	
Yan 2016	37	45	85	106	5.6%	1.14 [0.46, 2.81]	
Total (95% CI)		**5151**		**7775**	**100.0%**	**1.89 [1.39, 2.56]**	
Total events	925		800				

Heterogeneity: Tau² = 0.22; Chi² = 65.43, df = 12 (P < 0.00001); I² = 82%
Test for overall effect: Z = 4.06 (P < 0.0001)

0.01 0.1 1 10 100
Higher arrhythmia with NG   Higher arrhythmia with AH

FIGURE 2 Forest plot for pooled overall arrhythmias between AH and NG
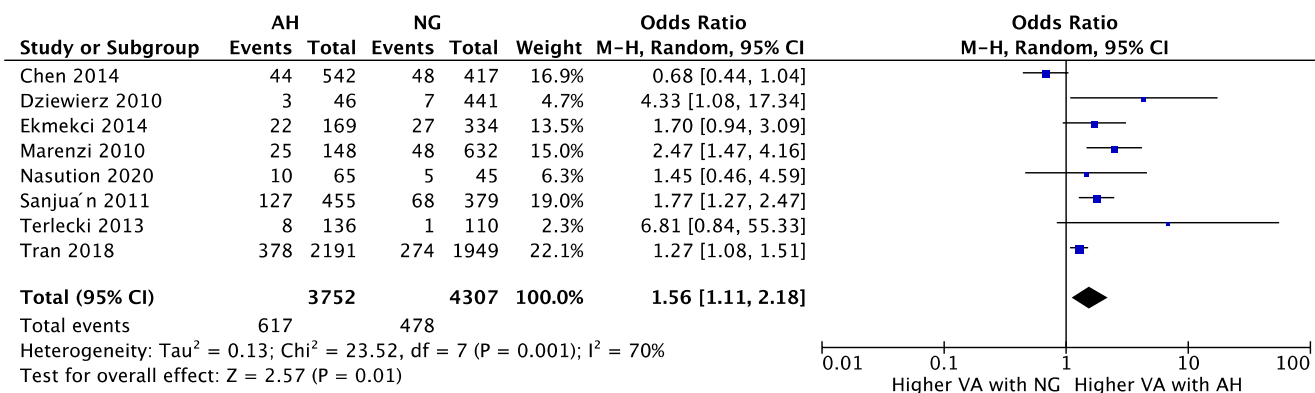
FIGURE 3 Forest plot for pooled VA between AH and NG
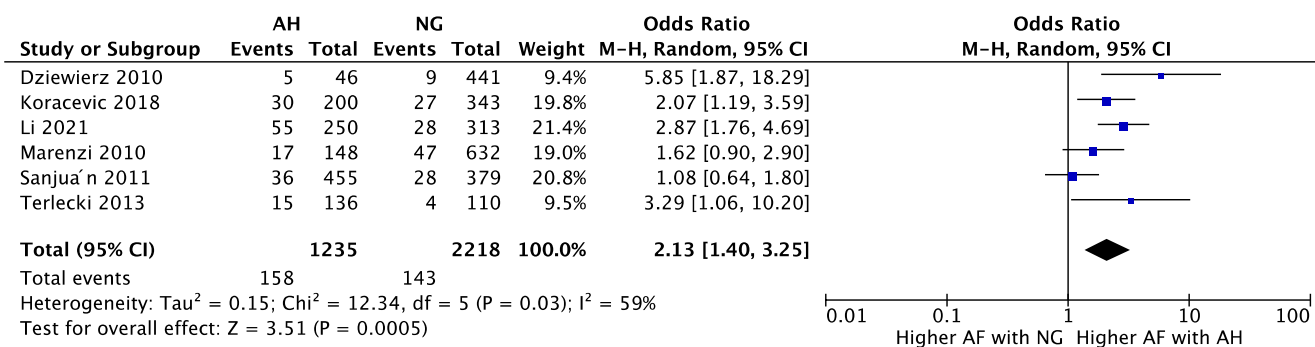

FIGURE 4 Forest plot for pooled new-onset AF between AH and NG

likely does not affect the outcomes as we performed a subgroup analysis of the different definitions, and the results were consistent with the main analysis. Third, we were able to do a subgroup analysis of DM status in only the primary outcome but not for other types of arrhythmias as we did not have enough data. The effect of hyperglycemia in patients with AMI on the different types of arrhythmias may be an area of future research. Finally, even though this meta-analysis included studies from several regions, more than half of included studies were from Asia with only one study from the United States. Additionally, we do not have studies from South America and Africa. So, it can lead to geographical bias.

5 | CONCLUSIONS

Our study suggested that AH was associated with an increased risk of arrhythmias in patients admitted with AMI, with and without a history of diabetes.

CONFLICT OF INTEREST

All authors have no competing interests.

ETHICAL APPROVAL

This is a systematic review and meta-analysis. No ethical approval is required.

DISCLOSURE

Authors declare no conflict of interests for this article.

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SUPPORTING INFORMATION